Amendments to the Claims:

Please cancel claim 1 and amend claims 3, 32 and 33 to read as follows. This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1-2. (Canceled).

3. (Currently Amended) The hybrid plasminogen activator as claimed in claim [[~~1~~]] 33, wherein the time lag ranges ~~rages~~ between 5 to 30 minutes.

4.-31. (Canceled).

32. (Currently Amended) A pharmaceutical composition comprising a genetically engineered hybrid polypeptide plasminogen activator of ~~claim 1 or~~ claim 33, and stabilizer(s).

33. (Currently Amended) ~~The hybrid polypeptide activator as claimed in claim 1~~ A genetically engineered hybrid polypeptide plasminogen activator comprising:

a) a streptokinase (SK) containing residues 16-383 of SEQ ID NO:2 ~~SEQ ID NO2~~, and

b) at least one [[~~the~~]] fibronectin finger-type fibrin binding domain (FBD) pair selected from: i) ~~pairs~~ FBD pair 1-2, residues 1-106 of SEQ ID NO:4; and [[~~or~~]] ii) FBD pair 4-5, residues 150-259 of SEQ ID NO:4,

said ~~at least one fibronectin finger-type binding domain (FBD)~~ FBD pair being bound to said streptokinase at its N or at its C-terminus.

REPLY

In further reply to the Final Office Action of December 16, 2004, Applicant submits the following remarks.

Applicants submitted an amendment on February 11, 2005 seeking to overcome all rejections by referencing sequence identification numbers in the claims. In the advisory action mailed March 9, 2005, the Examiner refused to enter the amendment. Based on an exchange of voice mails and a phone conversation with the Examiner, the undersigned understands that the primary basis for the refusal to enter the amendment is that the Remarks accompanying the February 11, 2005 Amendment failed to point out specifically the basis in the specification for the precise sequences identified in the claim as FBD 1,2 and FBD 4,5.

Applicant now presents the same amendment and points out the following basis for that amendment.

As detailed below, Fig. 6 (SEQ ID NO:4) is the amino acid sequence of human fibronectin FBD's.[1] The SK-FBD hybrids reported in the specification (specifically hybrids designated as SK-FBD 1,2 and SK-FBD 4,5) were made from a plasmid containing the coding sequences represented in Fig. 6 (SEQ ID NO:4).[2] As also detailed below, the sequences present in FBD (1,2) and FBD (4,5) are established in the specification as filed.

I. FBD(1,2) has the sequence of amino acids 1-106 of SEQ ID NO:4

The sequence of FBD 1,2 can be determined from the two primers used to obtain the FBD pair 1,2 by PCR from the FBD sequence (Fig. 6 and SEQ ID NO:4). Those primers are MY-10 and MY-6 (see page 45 of the specification as filed).

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[1] At page 12., line 11, the specification says, "Fig. 6. DNA and protein sequence of the gene-segment encoding for FBDs of human fibronectin...."

[2] ... cDNAs corresponding to the complete FN mRNA were prepared and cloned in several vectors [omitting citation to Kornhblitt et al.]. One such plasmid (pFH6) contained the entire sequence coding for the FBDs of the N-terminal region of human FN (as **represented...in Fig. 6** showing the amino acid sequence of the FBD regions contained in this plasmid....) Plasmid pFH6 served as the source for these sequences in the construction for the SK-FBD hybrids. Page 22, lines 2-9 of the specification.

At page 45, upstream primer MY-6 has the following sequence hybridizing with FBD(1,2): 5'-GAT GGT ACA GCT TAT TCT-3'. That sequence hybridizes as follows to the codons numbered 101-106 in SEQ ID NO:4:

AGA ATA AGC TGT ACC ATC

3'-TCT TAT TCG ACA TGG TAG -5'

Accordingly, the last amino acid residue in FBD pair 1,2 is ile at position 106 in SEQ ID NO:4 (Fig. 6), encoded by codon ATC.

At page 45 the specification discloses that the upstream primer MY-10 hybridizes to the TG-recognition site naturally present in the FN gene just at the beginning of the FBD-1 domain (citing Fig. 6). The hybridizing sequence is 5'-CAG GCG CAG CAA ATG GTT-3'. This corresponds to the beginning of the FBD sequence in Fig. 6: CAG GCT CAG CAA ATG GTT.[3] It is therefore clear that the first amino acid residue of FBD pair 1,2 is gln at position 1 of Fig. 6, encoded by codon CAG.

The above information from the specification as filed unambiguously establishes the end points and the entire sequence of the FBD pair 1,2. This information can be confirmed by reference to Fig. 19b, which includes DNA sequencing data of the SK-FBD 1,2 hybrid cassette in a T7 expression vector. The 318 bases (106 codons) starting at base 1341 and extending through base 1658 of Fig. 19b correspond to codons 1-106 of Fig. 6, which encode residues 1-106 of SEQ ID NO:4. Bases 1659-1601 are stop codon TAA.

II. FBD(4,5) has the sequence of amino acids 150-259 of SEQ ID NO:4

Similarly, the specification as filed unambiguously provides the sequence of FBD(4,5) from the sequence of the primers MY-13 and MY-14. At page 37, at the bottom note in the sentence carrying on to page 38, the specification explains (emphasis is added),

> The start of the hybridizing sequences in primer MY-13 correspond to the beginning of the sense strand sequence of FBD (4,5) namely **residue 150 onwards** (refer

[3] As shown in the underlining above, the second codon in MY-10 is GCG rather than GCT (as in codon 2 in Fig. 6). Both codons (GCG in MY-10 and GCT in Fig. 6) code for ALA at position 2 in FBD (1,2), so there is no ambiguity about the amino acid sequence recited in the claims.

to Fig. 6 for the amino acid sequence and DNA sequence of the fibrin binding domains of human fibronectin).

The primer sequence for primer MY-13 (page 37 of the specification) is 5' CCC ATA GCT GAG AAG TGT TTT GA-3', which corresponds to codons 150 – 156 (plus two bases of codon 157) of Fig. 6 (SEQ ID NO:4). So the first amino acid residue of FBD 4,5 is pro encoded by codon 150 (CCC).

The reverse primer sequence (MY-14) AGC AAC ATC GGT GAA GGG hybridizes to CCC TTC ACC GAT GTT GCT, codons 254-259 of Fig. 6, (SEQ ID NO:4). The note at the bottom of page 37 of the specification goes on to say,

> In the case of primer MY-14, the beginning of the hybridzing sequence (antisense) correspond exactly to the **codon for residue 259** of human fibronectin (Cf. Fig. 6).

So the sequence of FBD pair 4,5 extends from codon 150 through and including codon 159 of Fig. 6 (SEQ ID NO:4).

Further confirmation of the sequence of FBD pair 4,5 is found in Fig. 17b of the application as field. Figure 17b is DNA sequencing data of SK-FBD(4,5) hybrid cassette in the T7 expression vector. Note that the codons for residues 150-259 of SEQ ID NO:4 are given in Fig. 6, and they correspond to bases 1209-1538 of Fig. 17b, after which there is a TAG stop codon. This sequence is further confirmed by the fact that the sequence prior to base 1209 is not found in Fig. 6 and does not code for the polypeptide sequence in SEQ ID NO:4, confirming that FBD pair 4,5 does not start prior to residue 150.

In view of the foregoing the specification as filed clearly discloses the sequence of FBD pair 1,2 and FBD pair 4,5 as used in the experiments reported in the specification, and there is basis for the current amendment.

Enclosed is a $120.00 check for the Petition for Extension of Time fee. No further fees are believed to be due. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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John W. Freeman, Esq.
Reg. No. 29,066

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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